A Bayesian Regularized Artificial Neural Network for Simultaneous Determination of Loratadine, Naproxen And Diclofenac in wastewaters

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ABSTRACT

Simultaneous determination of medication components in pharmaceutical samples using ordinary methods have some difficulties. Chemometric methods are effective ways to analyses several components simultaneously. In this paper a novel approach based on Bayesian regularized artificial neural network (BRANN) is developed for determination of Loratadine, Naproxen and Diclofenac in water using UV-Vis spectroscopy. A dataset is collected by performing several chemical experiments and recording the UV-Vis spectra and actual constituent values. The effect of different number of neuron in hidden layer was analyzed based on final mean square error, and the optimum number was selected. Principle Component Analysis (PCA) was also applied on the data. Other back-propagation methods, such as Levenberg-Marquardt, scaled conjugate gradient and resilient backpropagation are tested. The results showed that bayesian regularization algorithm has the best performance among other methods. In order to see the proposed network performance, it was performed on two cross-validation methods, namely partitioning data into train and test parts, and leave-one-out technique. Mean square errors between expected results and predicted ones implied that the proposed method has a strong ability in predicting the expected values.

Key words: Bayesian regularized artificial neural networks (BRANNs), Loratadine, Naproxen, diclofenac, UV-Vis spectroscopy, Bayesian regularization algorithm, Principle Component Analysis

1. INTRODUCTION

Recently due to extensive using of various drugs and releasing of them through excreta, disposal of expired or unused medicine in environmental waters, and also toxicity of many drugs and their effects on the aquatic ecosystems, therefore, it is very important to determine the values of drug pollutants in waters (Boxall et al. 2012). Naproxen, 6-methoxy--methyl-2-naphthyl-acetic acid (Boynton et al.,1988), is a non-steroidal anti-inflammatory medicine and is widely used as an effective pain reliever. It is also used to reduce difficulty due to conditions such as kidney stones, rheumatoid arthritis and other inflammatory rheumatic

diseases, musculoskeletal disorders and gout (Elsinghorst et al., 2011; Sun et al.,2009). Several methods have been proposed for the determination of Naproxen in different mixtures (Sidelmann et al., 2001; Baeyens et al., 1995). Loratadine(4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-b]pyridine-11-ylidine)-1-piperidinecarboxylic acid ethyl ester) is an antihistamine medicine used as first-line agent for the treatment of urticarial and allergic rhinitis (Haria et al., 1994; Kay et al., 1999). Several methods have been described for estimation of Loratadine by various methods (Dhavale et al.,2008; Gandhi et al., 2008; Taha et al., 2009). Diclofenac [2-(2,6-dichlorophenylamino) phenyl)] acetic acid is an anti-inflammatory, anti-peritoneal and non-steroidal analgesic medicine (Lala et al.,2002; Mazurek et al., 2006). Some analytical models have been employed for the quantification of Diclofenac (Yang et al.,2008; Payan et al.,2009). Most of these methods have some difficult such as using of hazardous reagents, some derivatization, expensive and time consuming. Spectroscopic methods are very simple and applicable in qualitative and quantitative analysis of medicines (Benoudjit et al., 2004). UV-Vis spectroscopy is a simple, low cost, sensitive and available method for qualitative determination of targets. One of restrictions in spectroscopic studies is simultaneous determination of analytes that have overlap with each other (Altiokka and Kircali, 2003; Raggi et al., 1998).

Chemometric methods can provide us effective models for analyzing several components simultaneously. These models can determine components in the overlapped signals. Recently, methods such as principal components analysis (PCA) and partial least squares (PLS) have used frequently for multi-component determination (Abbasi-Tarighat , 2014). Quantitative spectrophotometry can be improved by using multivariate statistical methods, including artificial neural networks.

By progressive improvements in information technology and statistical methods, very useful quantitative and qualitative information from datasets, which is not obvious otherwise. The application of statistical methods to spectroscopic analysis has been steadily increasing in recent years, but is currently limited to classical chemometry. Some methods with excellent abbilities have been introduced and successfully applied on some difficult prediction and optimization problems (Wu and Olson, 2008; Asadabadi et al., 2009; Heshmati et al., 2009). The development of new alternative chemometric methods is one of the concerns in analytical chemistry. Mostly, new combined mathematical techniques are providing more accurate results than classical methods (Dinç et al., 2006; Dinç , Kanbur and Baleanu, 2007; Dinç, 1999; Dinç, Baleanu, 2008). Because repeating chemical experiments are expensive, it is very interesting to reach into acceptable accuracy using least number of training samples. Nonlinear calibration techniques, particularly using Neural networks try to achieve the expected accuracy level by faster convergence (Abhisek and Bernasconi, 2012).

The aim of the this research is to develop a simple, precise, accurate, sensitive and environmental friendly UV spectrophotometric method for determination of the pharmaceutical components using Bayesian regularized artificial neural network.

2.Experimental

During the experiment, analytical reagent grade chemicals and deionized water have been used. Stock standard solution of medicines was prepared and ternary mixture solutions were prepared by appropriate dilution of stock solution.

2.1 INSTRUMENTATION

Spectral measurements were conducted using a UV-visible spectrophotometer (Varian-Cary Win UV 100). The spectrum was scanned in the wavelength of 350–750 nm, for each concentration,. The random concentration of three analytes were obtained by Minitab program. 20 experiments is performed and hence a total number of 20 spectra, as well as the analyte values were obtained. Depending on cross-validation method, some of them will be used for training the intelligent network, and others for evaluating its performance.

2.2 COMPUTATIONAL METHODOLOGY

In this research, data treatment and network training and testing were done using MATLAB 2014b program under an Intel CORE i7 processor laptop having 8 GB of RAM. Network optimization was done by applying different number of neurons in the hidden layer and selecting the best backpropagation technique.

2.2.1 ARTIFICIAL NEURAL NETWORKS

Recently, the application of Artificial Neural Networks (ANNs) to chemical engineering and analytical chemistry and has risen rapidly for different applications such as calibration, molecular dynamics, interpretation of spectra, optimization of the linear signal range, modeling structure of protein, etc. (Rezaei, Ensafi and Shandizi, 2001; Zupan J, Gasteiger, 1991 and 1993; Cirovic, 1997). ANN is a computer system that consists of some simple processing elements (called neurons, compare to real neural system) that communicate with each other through axonic connections and handle data with its dynamic statistical response to inputs. Each neuron contains an input, weights associated with each input, transfer function, and the output (Mutihac and Mutihac, 2008). The advantage of ANNs is

maintaining their performance even in existing large amounts of noise in the input data. This characteristic makes it suitable for modeling the multivariate calibration. The structure of ANN algorithm with three layers, input, output and hidden layer is shown in the figure 1.

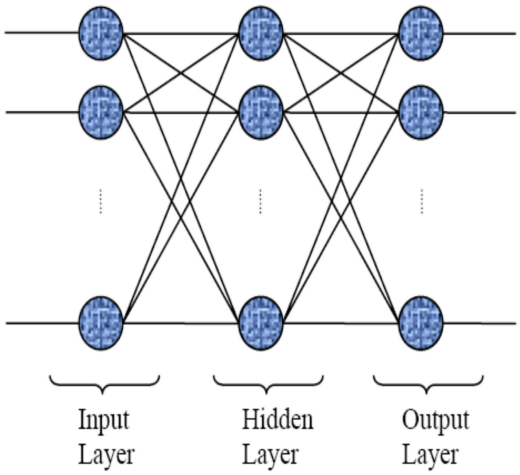


Figure 1: Architecture of the ANN

The number of neurons in input layer should be equal to the length of input data. It could be reduced to the number of PCs by using principle component analysis. The number of neurons in hidden layer is subject to change, the optimum number will be found experimentally in this paper. The output layer should be connected to the outputs (targets), hence it's number of neurons should be as the number of them.

2.2.2 BAYESIAN REGULARIZED ARTIFICIAL NEURAL NETWORKS (BRANNS)

Despite the ability of the ANNs in prediction, they suffer from the lack of a direct way to determine their optimum topology, Therefore, their performance is critically depends on the initial weights and training and test sets (Ruiz-Aguilar et al., 2017). Backpropagation (BP) is a method used in artificial neural networks which calculate the gradient needed to define the weights used in the network. The gradient descent optimization algorithm is generally used for backpropagation to control the neuronal weights by calculating the loss function gradient and minimizing the error function. Combination weights that minimizing the error is considered as the solution of learning problem (Rojas, 2013). It is most widely used in

supervised learning cases, where some example input-target pairs exist to measure errors between predicted values to actual values. Different backpropagation techniques are introduced for training neural networks (neuraldesigner.com; Saini, 2008). Some of them are: Levenberg-Marquardt backpropagation, resilient backpropagation and scaled conjugate gradient backpropagation.

A major problem of most backpropagation techniques is the probability for overfitting and overtraining which may cause to fitting to the noise, falling in local optima points, instead of global optima points and jeopardizing the generalization of the network. Bayesian regulation backpropagation is a mathematical technique developed by (Burden and Winkler, 2008) as a technique for automatically determining regularization parameter to reduce the potential for overfitting and converting nonlinear systems to ‘‘well posed’’ problems (Ticknor, 2013). In this method, the cost function *F* can be defined as

$$F = \gamma E_D + (1-\gamma)E_w \qquad (1)$$

where, γ is the performance ratio parameter, E_D is the sum of squared errors and $E_w = \|w\|^2/2$ is the sum of square of the network weights. In the Bayesian network, the density function weights variables could be written according to the Bayes' rule, because they are selected randomly [43]. Consider $D = \{x_m, t_m\}$ be the input-target pairs which will be used as training dataset. The posterior probability distribution for the weight $p(w|D,\gamma)$ is given as:

$$P(w|D,\gamma) = \frac{P(D\,|\,w,\gamma)P(w\,|\,\gamma)}{P(D\,|\,\gamma)} \qquad (2)$$

where, $P(D\,|\,w,\gamma)$ is the likelihood function, $P(w\,|\,\gamma)$ is the prior distribution, and $P(D|\,\gamma)$ is a normalization factor, which guarantees that the total probability is equal to 1. In Bayesian framework, the optimal weight should minimize the cost function in (1) which means maximizing the posterior probability $P(w|D,\gamma)$. The performance ratio parameter γ could be optimized by applying the Bayes' rule:

$$P(\gamma|D) = \frac{P(D\,|\,\gamma)P(\gamma)}{P(D)} \qquad (3)$$

By assuming a uniform prior density $P(\gamma)$ for γ, the posterior probability could be maximized by maximizing the likelihood function $P(D\,|\,\gamma)$. Considering the Gaussian form for all probabilities, $P(D\,|\,\gamma)$ can be expressed as:

$$P(D|\gamma) = \left(\frac{\pi}{\gamma}\right)^{-\frac{N}{2}} \left[\frac{\pi}{1-\gamma}\right]^{-\frac{L}{2}} Z_F(\gamma) \qquad (4)$$

where, L is the total number of parameters in the neural network. Let F has a single minimum value as a function of w at w* and has the shape of a quadratic function in a small band around that point, then $Z_F(\gamma)$ can be approximated as:

$$Z_F(\gamma) = (2\pi)^{L/2} det^{-1/2} H^* \exp(-F(w^*)) \quad (5)$$

Where, $H = \gamma\nabla^2 E_D + (1-\gamma)\nabla^2 E_w$ is the Hessian matrix of the objective function. By substituting the $Z_F(\gamma)$ into equation (4), the optimum value of γ at the minimum point could be determined. Authors in (Forsee and Hagan, 43) have proposed a Gauss–Newton approximation to the Hessian matrix which is applicable if the Levenburg–Marquardt training algorithm is used to find the minimum. This technique reduces the risk of falling in local minima, thus increases the generalizability of the neural network.

Kayri in (Kayri, 2016) is compared predictive ability of Bayesian regularization with levenberg–Marquardt artificial neural networks and showed that Bayesian regularization have better performance and can provide a robust model for quantitative studies. Shao et. al have shown that Bayesian regularized artificial neural networks (BRANNs) have usually better performance than traditional back-propagation neural networks because of their ability in controling the complexity of the model (Shao, 2005). Aguilar, López and Turias (Ruiz-Aguilar et al., 2017) have used BRANNs as the best artificial neural network, in their research. In order to see its performance in this study, all BP methods will be evaluated and compared together.

2.2.3 PRINCIPLE COMPONENT ANALYSIS (PCA)

PCA is a good way to extract features and reduce dimensions. At PCA, we try to show dimensional data in a space of lower dimensions that reduces the complexity of space and time. First, the vector μ of the d-dimensional mean and the d-dimensional covariance matrix Σ are calculated for the data. Then the special characteristics and Eigen values are calculated and organized in ascending order. Next, the largest K characteristics are selected, which are based on a spectrum of special characteristics, and most of their dimensions indicate the inherent dimensions of the underlying space of the signal. Other dimensions are noise. As a result, the matrix $k * k$ contains the column k of the special property and we have (Subasi and Gursoy, 2010):

$$x' = A^t(x - \mu) \qquad (6)$$

2.2.4 CROSS-VALIDATION

Cross-validation is technique for evaluating models used in prediction problems, in order to estimate how accurately a predictive model will act in practice or how the results of a statistical model will act in a separate dataset. One type of cross-validation is partitioning method, where the dataset is divided into two parts, namely training subset and validation (or test) subset. The model is trained by training dataset, and then the model is evaluated by analyzing test subset. In order to reduce variability, normally the partitioning procedure is repeated enough and the results are combined or averaged (Kohavi, 1995; Pérez, Fernández and Marco; 2018).

Leave-one-out validation method is another way that used in this research, where in each iteration one experiment is considered for test and the neural network is trained by other residual experiments. This procedure is repeated as the number of experiments, so that each experiment get the chance to be selected as the test once.

3.RESULTS AND DISCUSSION

The structure of Loratadine, Naproxen and Diclofenac is shown in Figure 2.

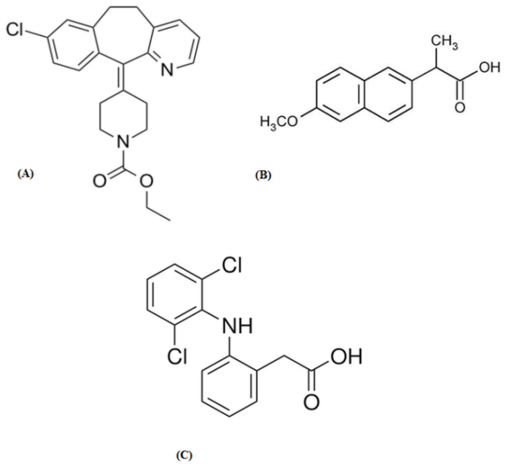


Figure 2 .Structure of (A) Loratadine (B) Naproxen and (C) Diclofenac

Also the UV-Vis spectra of these analysts are depicted in Figure 3. As can be observed from it, their spectra is overlapped with each other.

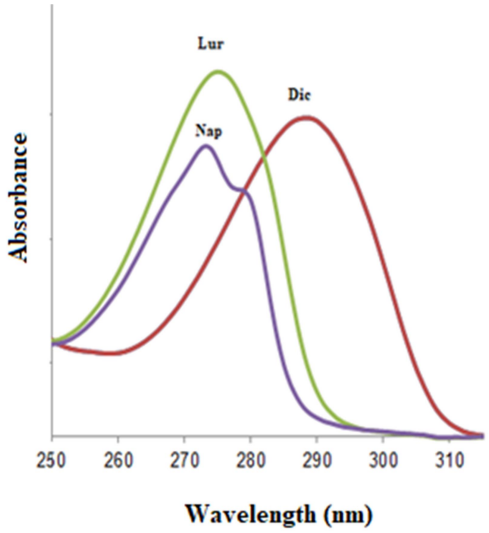
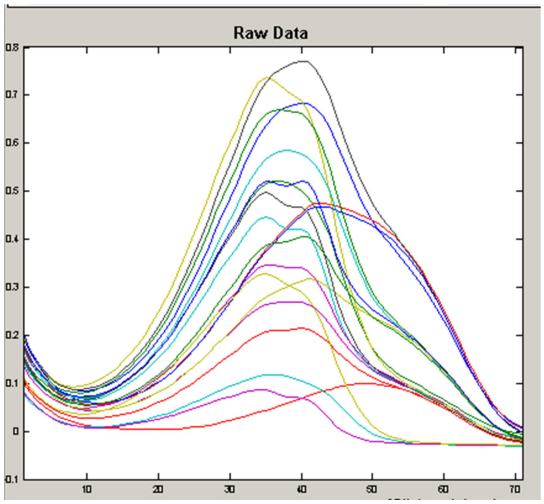


Figure 3 . The UV-Vis spectra of Loratadine, Naproxen and Diclofenac

The linearity of the analytical method was its ability to elicit test results which are directly proportional to analyte concentration in samples within a given range. The linear range of Loratadine is about 4-40 ppm (Ganorkar et al, 2011) Diclofenac 5-25 ppm (Gunji, Nadendla and Ponnuru, 2012) and Naproxen 5-25 ppm (Hashim Zuberi et al 2014). Therefore ternary mixtures of medicines were prepared in these linear range.

In order to develop an intelligent network for predicting the unknown values, the recorded dataset compromising of 20 data series of UV-Vis spectra and actual values of Loratadine Naproxen and Diclofenac in different ternary mixtures is used. Some pre-processing steps may improve the prediction of concentrations. Normalization technique is used in this research. Figure 4 Is showing the data before and after normalization.



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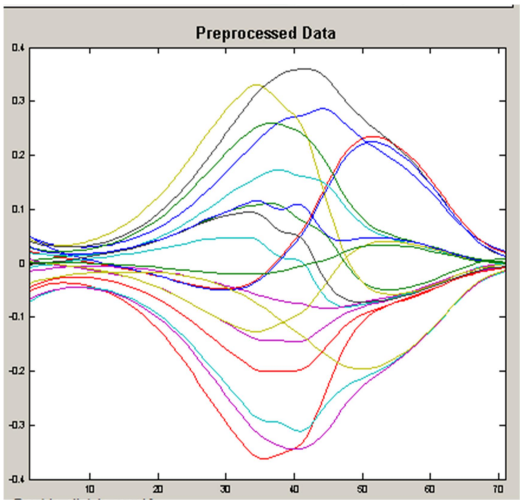


b)

Figure 4: Pre-processing step, a)Raw data, b)normalized data

Table 1 and Figure 5 is showing the result of applying PCA on experimental data for different numbers of PC. As it shown around 80% covariance is achieved by selecting the first PC only, and 98.5% cumulative variance is feasible by selecting two strongest PCs. The cumulative variance will be very closed to 100% by selecting 6 or more PCs.

Table 1: Principle components analysis of the data

# of PC	Eigenvalue of Cov(X)	% Variance This PC	% Variance Cumulative	RMSEC

1	56.9111	80.1564	80.1564	0.43418
2	13.0752	18.4158	98.5722	0.11646
3	0.58043	0.8175	99.3897	0.076142
4	0.33392	0.47031	99.86	0.036464
5	0.083014	0.11692	99.977	0.014794
6	0.016193	0.022808	99.9998	0.001482
7	7.91E-05	0.000111	99.9999	0.001067
8	2.36E-05	3.32E-05	99.9999	0.000907
9	1.97E-05	2.77E-05	99.9999	0.000748
10	1.27E-05	1.79E-05	100	0.000624
11	8.21E-06	1.16E-05	100	0.000529
12	5.61E-06	7.90E-06	100	0.000452

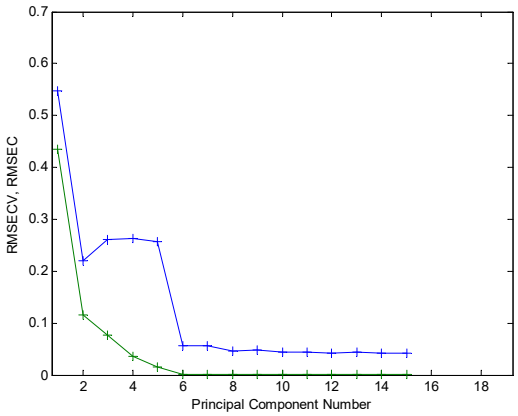


Figure 5: Eigenvalues and Cross validation Results

A common cross-validation method for estimating the generalized error in prediction models is partitioning. In this method the dataset is randomly divided into two subsets, one used for training and the other for testing. Normally, 70% of input data is selected for train and other remained 30% are used for test.

The following results were obtained by applying this cross validation method. Of the total data (20 samples), 70% (14 samples) were selected for training, 15% (3 samples) for validation, and 15% (3 samples) for testing. For evaluating the results, the above selections

were done randomly. Table 2 is showing the mean square error (MSE), as the average squared difference between outputs and targets, as well as regression R-values which measure the correlation between outputs and targets. Ideal values for these parameters are one and zero, respectively. As it shown they implies acceptable prediction.

Table 2: MSE and R-values between actual and estimated values

Results

	Samples	MSE	R
Training:	14	4.33941e-6	9.99999e-1
Validation:	3	1.21608e-0	9.81809e-1
Testing:	3	3.46381e-0	9.56483e-1

Figure 6 Is showing the estimated formula and regression between output and targets in different parts (training, test, validation and all data groups).

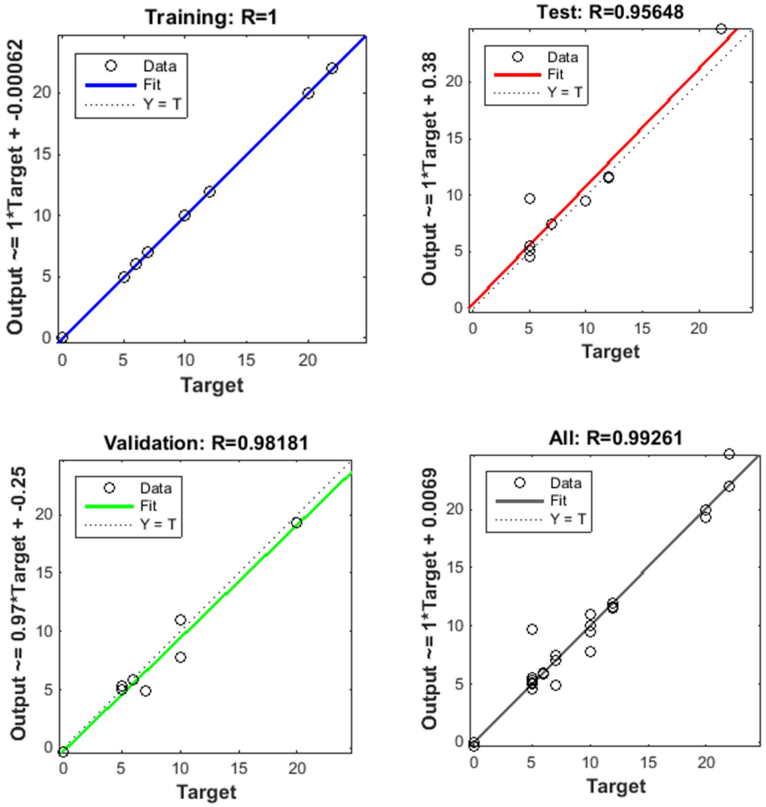


Figure 6: Regression between outputs and targets in different groups

LEAVE-ONE-OUT RESULTS

In order to see more tangible prediction results, Leave-one-out cross-validation method is used in this part. In this method, one experiment data is retained for test, and the ANN network is trained by other 19 experiments. The prediction results of the remained experiment is compared by its actual values. This procedure is repeated as the number of experiments, so that all experiments involved as test for one time.

4.2.1 ADJUSTING NEURAL NETWORKS PARAMETERS

Two important parameters of artificial neural networks are number of neurons in hidden layer, and backpropagation method. Effect of these parameters is evaluated experimentally. In order to see the effect of hidden neuron numbers, the leave-one-out algorithm is performed separately for different numbers of hidden neurons. The average of three concentration MSEs is calculated as the index of prediction total error. Average MSEs is plotted in in Figure7 with respect to number of neuron numbers in hidden layer. As shown the average MSEs is very high by selecting one neuron in hidden layer. The best value is achieved by selecting 3 neurons is hidden layer.

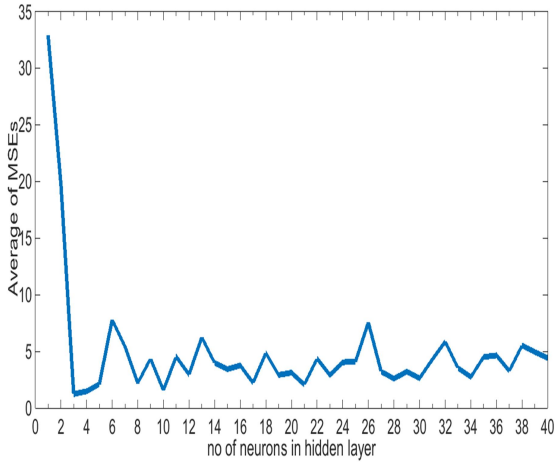


Figure 7: Average of MSEs in different number of hidden neurons

In order to see the network training function, different backpropagation (BP) algorithms is applied. The results is shown in table 3. As it shown, the minimum average MSE is achieved by using Bayesian regularization algorithm, hence this method is used in this research.

Table 3: Effect of different training algorithms

Network training Function	MSE lur	MSE nap	MSE dic	Average
Bayesian regulation BP	0.6926	0.415	0.485	**0.531**
Levenberg-Marquardt BP	2.558	0.127	1.05	1.245
Scaled conjugate gradient BP	0.8433	0.274	0.702	0.606
Resilient BP	2.3785	0.859	1.459	1.566

After adjusting the parameters and selecting BRANN as the best one, the network is tuned to predict the unknown values. Figure 8 is showing an example performance of the network where the 20^{th} experiment is left as test.

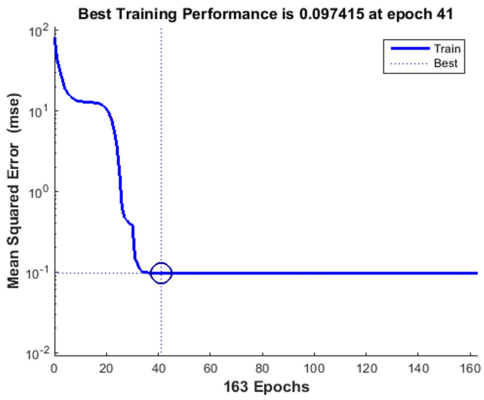


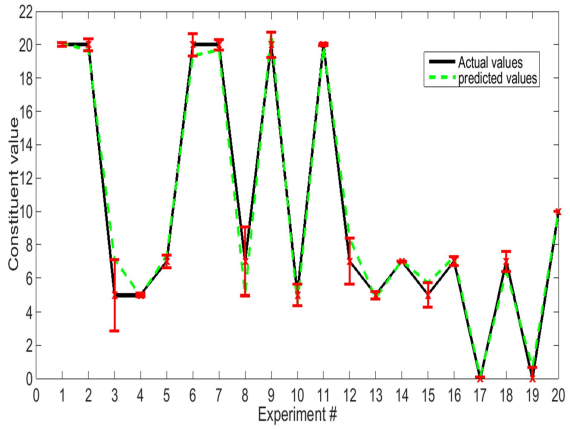
Figure 8: the performance of the network when 20th experiment is left for training

The final prediction results of the algorithm is shown in table 4. The values of individually prediction of each row is compared by its actual values. The total MSE values is shown at the end row. Figure 9 is showing the actual and predicted values and their error bars. As implied by comparing the values, the designed model could predict the values by acceptable accuracy.

Table 4 Prediction values versus real values

	Actual values			predicted values		
Exp no	**lur**	**nap**	**dic**	**lur**	**nap**	**dic**
1	20	5	22	20.114	4.644	20.123
2	20	5	6	19.653	5.119	7.065
3	5	5	22	7.120	5.294	22.652
4	5	20	6	4.922	19.607	6.391
5	7	10	6	7.369	10.434	6.338
6	20	20	6	19.339	18.192	6.080
7	20	10	22	19.679	9.486	22.967
8	7	5	22	4.955	5.145	21.479
9	20	10	12	20.767	10.747	11.985
10	5	5	6	4.376	4.165	5.662
11	20	5	12	19.929	4.857	11.682
12	7	5	6	8.387	4.677	6.299
13	5	5	12	4.799	5.101	13.173

14	7	20	6	7.033	20.410	5.617
15	5	20	12	5.700	20.151	11.570
16	7	10	12	7.263	9.521	11.854
17	0	0	7	0.119	0.402	6.328
18	7	0	0	6.406	1.356	0.215
19	0	7	0	0.686	6.394	0.252
20	10	10	0	10.013	10.056	0.771
	Average MSE			**0.693**	**0.415**	**0.485**



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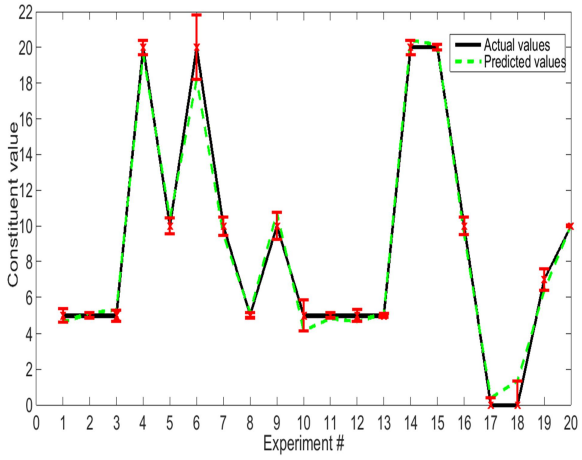

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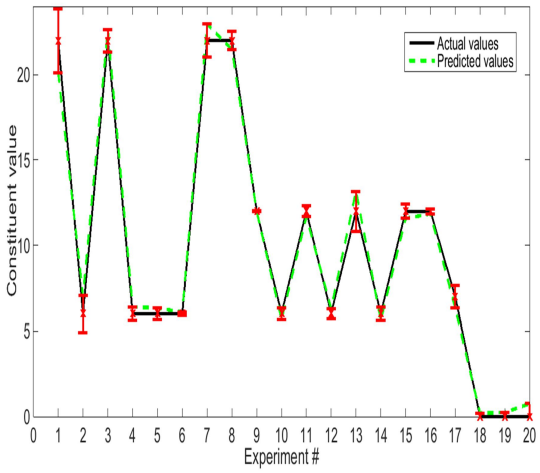

c)

Figure 9: Error bars between predicted and actual values, a) Loratadine, b)Naproxen and c)Diclofenac

2. CONCLUSION

Simultaneous determination of components in multi components medicine formulations is a difficult task, especially when the absorption spectra of the components are overlapped together. In this paper, an artificial neural network trained by the backespropagation learning was employed to predict Loratadine, Naproxen and Diclofenac in turnery mixtures. For this purpose, 20 chemical experiments were performed and a dataset compromising of UV-visible spectra and the absorbance values is made. A Bayesian regularized artificial neural network (BRANN) is proposed for prediction. Firstly, the 70% of the dataset is used for training the BRANN and two 15% of it for validation and testing. The results shown acceptable mean square errors and R-values. In the next step, leave-one-out cross validation method is applied. The best values of the number of neurons in the hidden layer is found. other backpropagation methods are also analyzed. Finally the optimized network is applied. The final results imply acceptable MSE between predicted values and actual values.

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Conflict of interest

All authors declare that they have no conflict of interest.

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